Does getting sick keep cattle healthy?

Undergraduate Research Thesis

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by

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Abstract

Foot-and-mouth disease (FMD) is an infectious, viral disease that impacts livestock worldwide. The disease is endemic in many countries, and outbreaks have had major economic impact, including the United Kingdom in 2001 (Knight-Jones and Rushton 2013). FMD is a major hindrance to the international trade of livestock and has forced countries to spend billions of dollars in prevention and control (Knight-Jones and Rushton 2013). The virus that causes FMD has 7 serotypes and many subtypes, with little vaccine efficacy between these serotypes (Waldmann and Trautwein 1926; Brooksby and Rogers 1957; Brooksby 1958; Jamal and Belsham 2013). However, in settings where multiple serotypes of FMD circulate regularly (endemic settings), infections with one type may prevent future disease through cross-immunity. As countries progress in their efforts to eradicate the disease, initially, we may see more FMD due to loss of this cross-immunity (Grenfell and Harwood 1997). This research poses the question: Could cross-immunity between FMD serotypes prevent FMD in endemic settings? To answer this question, we conducted *in silico experiments* with an agent-based modeling program called NetLogo in order to direct different simulations for cattle herds infected with two different serotypes of FMD: O and A. Another model was created to match the simulated infectiousness between herds to empirical data on infected cattle, and the results from this model were then applied to the herd model. We constructed and extensively checked the herd simulation method and ran simulations to test the effects of different levels of cross-immunity in the population. The results were analyzed to determine whether and how much cross-immunity might prevent transmission in endemic populations. From my simulation runs, we concluded that cross-immunity would not prevent FMD infections.

Introduction

Foot-and-mouth disease (FMD) is an infectious, viral disease that impacts livestock worldwide. FMD presents in animals as vesicles that burst and become erosions on the snout, teats, feet, and mouth of animals, and can lead to lameness and decreased milk yield in an infected animal (Grubman and Baxt 2004). The mortality rate for FMD is low except for deaths in young animals due to myocarditis, but FMD morbidity is high (Grubman and Baxt 2004; Ludi et al. 2016). While many countries have managed to remain FMD-free due to eradication and prevention measures, 75% of the human population resides in countries where FMD is endemic (Knight-Jones et al. 2016). The FMD virus is an icosahedral, non-enveloped, single-stranded RNA virus with a protein capsid, and the virus has 7 serotypes and many subtypes(Waldmann and Trautwein 1926; Brooksby and Rogers 1957; Brooksby 1958), which makes the identification of the specific serotype and subtype causing an infection through tests like virus isolation, reverse transcriptase PCR, structural protein ELISA, or virus neutralization tests a crucial step in controlling the disease (OIE Biological Standards Commission 2012). The virus serotypes can be differentiated by a structural polypeptide, VP1, in the capsid that aids in virus attachment and entry into the host, yet the virus is constantly evolving in such a way that serotype-specific vaccines can sometimes lose their efficacy (Jamal and Belsham 2013). In countries where more than one serotype circulates frequently, however, the decision on whether or not to vaccinate animals, which serotypes to include in the vaccine, and the level of vaccination with which to proceed is more difficult. With multiple serotypes circulating in an endemic setting, a natural cross-immunity between serotypes could exist, in which infection with one serotype could prevent further infections with another serotype. This interplay between FMD infections and cross-immunity was explored in my research.

While FMD is not a food safety or public health concern and is not associated with high mortality rates, the disease costs billions of dollars annually in prevention and control. For endemic settings, vaccination and production losses range from 6.5 to 21 billion dollars each year, whereas an outbreak in a traditionally FMD-free region could lead to annual losses of over 1.5 billion dollars (Knight-Jones and Rushton 2013). Vaccination, decreased milk production, livestock fertility issues, restricted herd movement, and the loss of local and international trade are all factors that could contribute to losses when met with a FMD herd infection (Knight-Jones and Rushton 2013), and these losses have been found to affect both governments and small herd farmers alike (Knight-Jones et al. 2016). In Cameroon specifically, a study found that FMD had infected roughly half of the herds surveyed, with greater incidence being found in mobile herds that were more likely to contact other herds (Bronsvoort et al. 2004). Another study corroborated this finding, as a lower incidence of FMD was observed in Cameroon sedentary herds that had fewer contacts with other herds (Knight-Jones et al. 2016). The high incidence of FMD, the lack of a prevention control program for FMD, and the negligible amount of FMD vaccination practiced in Cameroon make its environment and herd populations helpful to model when looking at hypothetical cross-immunity and multiple serotypes of FMD infections (Ludi et al. 2016). Therefore, the models created to answer my research question utilized herd demographics, simplified herd movement patterns, seroprevalence, seropositivity, and other FMD data from Cameroon to construct cross-immunity and other experiments.

Methods

NetLogo, a computer agent-based modeling program was used to simulate FMD infections on an individual cattle level for the cattle model and a herd level for the herd model (Wilensky Uri 2016). The cattle model was created in order to apply previously acquired data regarding FMD infections and immunities within individual Cameroonian cattle to the scale of many cattle herds in the herd model (Dahl and Hjort 1976). One herd of 100 FMD-susceptible individual bovines was placed in this simulation, matching the age and sex demographics of cattle herd data in Cameroon (Dahl and Hjort 1976)(Fig. 1). This herd was then infected with FMD using transmission and immune duration parameters calculated from Cameroonian data (Pomeroy et al. 2015). To ensure that all possible experimental outcomes would be observed, the simulation run was run 30 times for both of the serotypes, O, and A, for the duration of ten years, with the percent of cattle infected and immune being recorded daily. Each day in the simulation, individual bovines had a specified probability of reproducing, dying, or being sold that matched their age group and sex (Fig. 11). Colors of individuals were utilized to represent an individual bovine's disease status: susceptible, infected, and immune (Fig. 10).

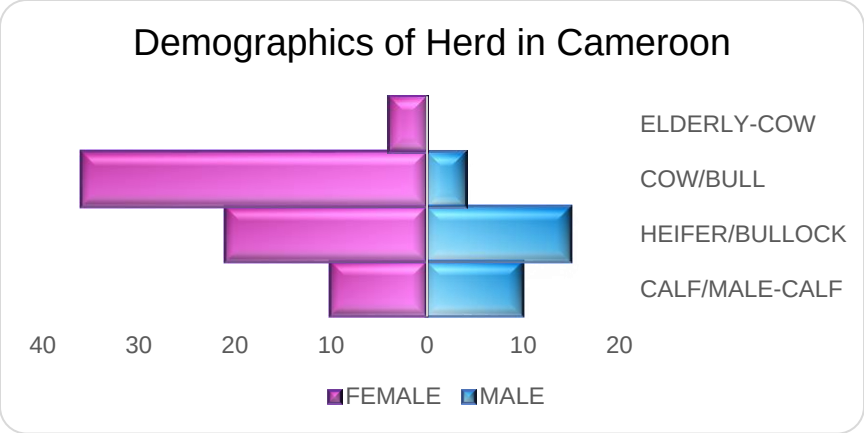

Fig. 1. Demographics of herd in Cameroon used in cattle model (Dahl and Hjort 1976).

To initiate the cattle model, one susceptible bovine within the herd was infected for 7 days with one of the two serotypes on the first day of the simulation. This infection prompted all other susceptible cattle within the herd to have a probability of becoming infected as long as there was at least one individual infected – this probability matched recorded Cameroon data that was converted to daily probabilities (Estrada et al. 2008; Pomeroy et al. 2015). Infected cattle would remain infected for 7 days, and then become immune to the serotype for a specific number of days that corresponded with the serotype immunity duration (Pomeroy et al. 2015). Once an individual's duration for immunity ended, the individual would return to being susceptible to the serotype. In order to simulate natural maternal immunity, if a female individual that had immunity to a serotype gave birth to a calf, this calf would have immunity to that serotype for one year. The individual infection and immunity lengths recorded from the cattle model were summarized for the entire herd and then entered into the herd model so that the herd remained infectious for a longer time than an individual animal and immune to infection for a shorter time than for an individual animal.

The herd model was created to determine the effect of cross-immunity on infections between mobile and sedentary herds in an endemic setting by utilizing Cameroon movement patterns and determined Cameroon herd infection and immunity lengths. The herd model simulation world had an area of 200 kilometers long and wide, with 4 zones of 60 kilometers by 60 kilometers that were 40 kilometers apart set up for the mobile herds to move within. Ten mobile herds and 1000 sedentary herds were placed in the simulation, following the known ratio of mobile to sedentary herds in Cameroon (Njoya et al.). Of those herds, 900 sedentary herds were spread randomly throughout the two lower quadrants and 100 were spread throughout the two upper quadrants, while mobile herds were assigned a movement pattern matching the zone numbers that they would move between, 3113, 3123, 4114, or 4124, and started out the simulation run in either of the defined zones 1 or 2 (Fig. 12). For example, if a herd's movement pattern were 3113, it would begin a simulation run in zone 1, move within zone 1 for a season, and then move to and within zone 3 for the next season. Mobile herds were split unevenly into the four movement patterns to represent the different distributions of Cameroon mobile herd movement, with 3 mobile herds each given patterns 3113, 3123, and 4114, but only one mobile herd having the 4124 pattern (Kim et al. 2016).

All herds in the model began the simulation run as susceptible to all serotypes, and all of the landscape patches, which represented 1 sq. kilometer and were used to show environmental persistence of FMD,

began as non-infectious environment. When the simulation run started, herds were given the same daily probability of dying and reproducing each day, 0.009%, which was converted from an annual probability of 3.4%, a percentage observed for Cameroon herd growth rates (Dahl and Hjort 1976). Mobile herd movement began, in which herds would move between the zones of their respective movement patterns at a designated time. Movement between zones would last for about 10 days, with herds moving about 10 kilometers each day. A mobile herd would then reach a set patch in the zone of their pattern, stop, and wait for another 65 days with an addition or subtraction of up to 7 days. This pattern of movement was continued for all ten years of the simulation run and was used as a simplification of herd movements between rainy and dry season pastures in Cameroon (Xiao et al. 2015; Kim et al. 2016).

Shortly after the start of the simulation, FMD infections were initiated. For serotype O infections, a mobile herd was infected on day 300. It was determined that an outbreak would be more likely when the mobile herd became infected during the time that mobile herds were moving throughout the densest area of sedentary herds (Pomeroy et al. 2017). This led us to begin the infection on day 300 with one mobile herd setting its disease status to infected with serotype O. Infected herds were then able to have a daily probability of infecting, 0.549%, any susceptible herds within a radius of 4.5 kilometers, and the environmental patch that was underneath an infected herd would become infected and be able to have a probability of indirectly infecting, 0.242%, any herd located on the patch for 9 days. Indirect infection probabilities were based on experimental data (Bravo de Rueda et al. 2015). The direct serotype-specific infection probability was determined by fitting herd model simulation runs to Cameroonian data using two equations (Fig. 3 and Fig. 4).

$$P(a) = \frac{\lambda(t)}{\lambda(t) + \omega}\left(1 - e^{-\int_0^t (\lambda(t)+\omega)dt}\right)$$

Fig. 3. Reverse catalytic equation used to calculate force of infection for O and A based on seroprevalence data from Cameroon (Pomeroy et al. 2015).

$\lambda(t) =$ annual per capita probability of infection

$\lambda(c) =$ probability of infection per contact

$P(c) =$ annual contacts per herd

$\lambda(c) = \lambda(t)/P(c)$

Fig. 4. Equations used to calculate the correct herd-level direct infection probability per contact where annual contacts per herd (P(c)) was calculated as the simulated number of contacts between infected and susceptible herds divided by the number of susceptible herds in the herd model.

In the simulation, I kept track of serotype-specific infection, immunity, and susceptibility for each herd each day with two different commands: “disease-status” and “SIM-run.” “Disease-status” allowed different serotype-specific infections to become visible by changing the colors of infected, immune, or susceptible herds. While the disease-status command helped visualize the serotype status of herds, the SIM-run command set the length of serotype infection and immunity for a herd. If a herd became infected with O or A, it would stay infected for a designated length of time: a normal distribution around 89 days for serotype O or a normal distribution around 10 for A. Once the herd was no longer infected, the herd would then stay immune to the serotype for a designated length of time: a normal distribution

around 1068 days for serotype O or a normal distribution around 2262 for A. At the end of this immune period, a herd would once again become susceptible to this serotype (Fig. 2). These infection and immunity lengths were taken from the simulations run in the cattle model.

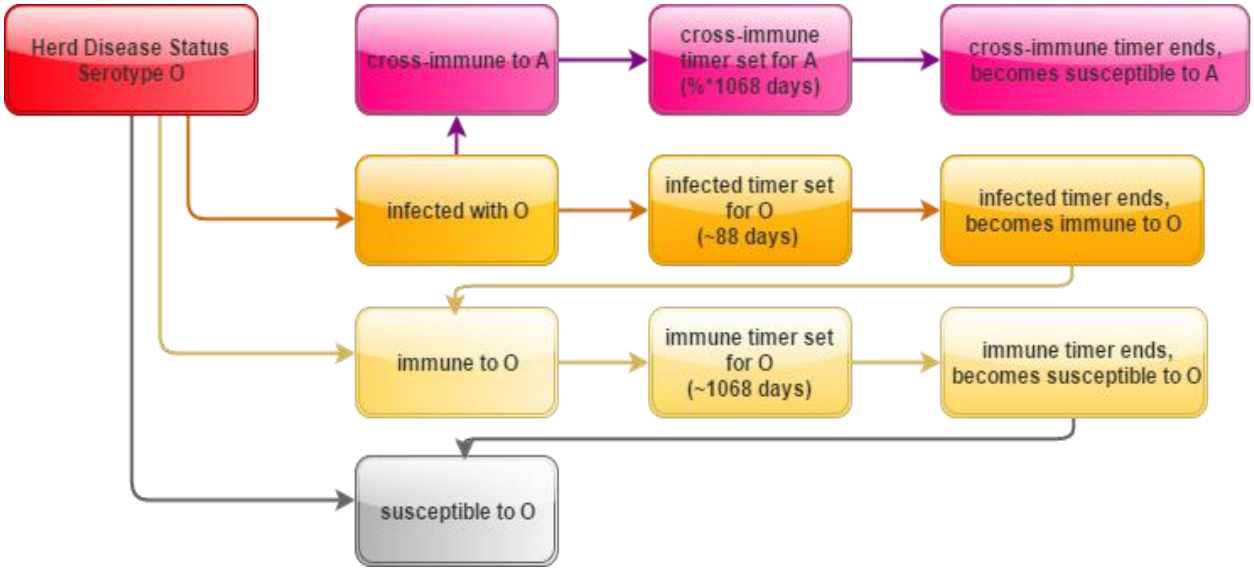

Fig. 2. Flowchart depicting serotype O SIM-run command.

Two sets of experiments were conducted before cross-immunity was tested: simulation runs to determine the probability of direct and indirect infections for O and A and homogeneous and heterogeneous mixing experiments to examine the role of distance in infection outbreaks as well as determine how many model runs were needed to observe all possible outcomes. For the direct and indirect infection probability experiments, the experiments were run in the herd model for a duration of 365 days and for 100 simulation runs each with differing amounts of infection probability for serotype O. These experiments were conducted in order to estimate the parameters of susceptible herd contacts with infected herds, total number of susceptible herds, and the unknown variable of per contact direct infection probability, equal to the O and A seroprevalence outcomes of the reverse catalytic equation (Pomeroy et al. 2015). The optimal per contact direct infection probability was calculated to be 0.549 for serotype O, and this value was used to scale the seroprevalences calculated for A per contact infection probabilities as well as indirect infection probabilities (Fig. 3 and Fig. 4).

For the homogeneous and heterogeneous mixing experiments, the per contact O serotype direct and indirect infection probabilities found in the previous experiments were used, and serotype O was introduced into the herd model's population. The homogeneous mixing experiment was run for 1000 simulations, and rather than allowing only susceptible herds within a 4.5-kilometer radius of an infected herd to have a chance of becoming infected, all herds in the population had the same chance of becoming infected regardless of the location of an infected herd (Fig. 13-15). This change in the susceptible herds that were able get infected was used to observe the effect that a designated infection radius for infected herds (heterogeneous mixing) would have on the dynamics of outbreaks compared to simulations without a designated infection radius (homogeneous). The heterogeneous mixing experiment was also run for 1000 simulation runs, but only susceptible herds within a 4.5-kilometer radius of an infected herd had a chance of becoming infected (Fig. 16-18). The homogeneous and heterogeneous mixing experiments were used to determine how many simulation runs were needed to

view all possible outbreaks. Two hundred simulations for both the homogeneous and heterogeneous mixing was determined to be the point at which there were no additional changes to how outbreaks occurred. The simulation times at which to introduce a second serotype infection were also established through the heterogeneous mixing experiments, as the initial rise, peak, and fall of serotype O immunity was recorded in these experiments.

In the cross-immunity experiments, serotype O was introduced at day 300, followed by an introduction of serotype A at day 401, day 494, or day 1714. The days at which serotype A would be introduced were determined during the heterogeneous mixing experiments. Cross-immunity was introduced at the same time a herd became infected with one serotype, so that if a herd's serotype status was infected for one serotype, it would become cross-immune to the other serotype and it could not become infected with the second serotype for which it had cross-immunity. Two sets of experiments were run for cross-immunity: cross-immunity for serotype A and cross-immunity for serotype O. For serotype A cross-immunity experiments, if a herd became infected with serotype O, it would become cross-immune to serotype A (Fig. 2). The reverse was true for serotype O cross-immunity experiments: if a herd became infected with serotype A, it would become cross-immune to serotype O. Cross-immunity for one serotype was varied as a percentage of the immunity length of the serotype that infected a herd. For instance, if cross-immunity for A were to be at 20%, then the length of serotype A cross-immunity in a herd infected with serotype O would be 20% of 1068 days, or 214 days. The cross-immunity for A and cross-immunity for O experiments were run for 200 times each with cross-immunity at 0%, 20%, 40%, 60%, 80%, and 100%. Results regarding percent of herds infected with O and herds infected with A for these cross-immunity experiments were recorded and analyzed.

Results

Model Parameters

Cattle model simulation runs for serotypes O and A recorded the length of O infection and immunity length within one herd of cattle as 89 and 1068 days and the length A infection and immunity as 10 and 2262 days. The infection lengths of O and A were recorded as the lengths of time that at least one individual was infected with a serotype. The immunity length of O was recorded as the length of time when over 50% of the population in the simulation runs were immune to serotype O, but this same criterion was not applied to A because the number of herds infected and immune to this serotype never rose above 50%. This criterion was an attempt to mimic the percentage of individuals in a herd required to prevent future infections, 94% for serotype O, but the proportion of serotype immune individuals never reached this level of immunity (Pomeroy et al. 2015). For serotype A immunity length, the length of time that at least one individual was infected with serotype A was used.

In the initial experiments of the herd model used to find per contact infection probabilities, the per contact infection probabilities for serotype O and A were calculated to be 0.549% and 0.064% (Fig. 3 and Fig. 4). From these direct infection probabilities, indirect infection probabilities via the environmental patches were calculated to be 0.242% and 0.0282% for O and A due to previous research that found indirect transmission of FMD to be 44% of the direct transmission rate (Bravo de Rueda et al. 2015).

For homogeneous and heterogeneous mixing, the minimum number of simulation runs needed to be run to ensure that all relevant outcomes had been recorded was determined to be 200 simulations for both homogeneous and heterogeneous. This number of simulation runs was the point at which the

standard deviation of the maximum number of herds infected and immune with serotype began to level off (Fig. 5 and Fig. 6). One outlier in the homogeneous mixing simulations failed to have an infection take place, and it was excluded in the analysis (Fig. 14 and Fig. 15).

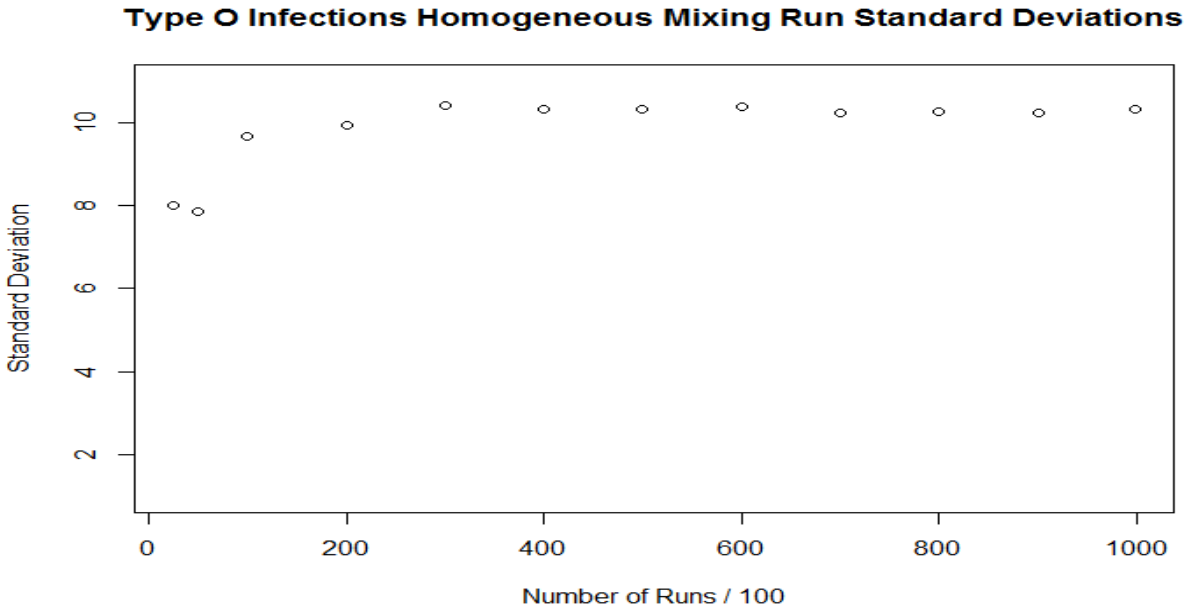

Fig. 5. Homogeneous Mixing Experiment – standard deviation of the maximum number of herds infected between runs. Looking at this figure, the point at which the standard deviation among maximum number of herds infected begins to level off starts around 200 runs. All future experiments containing homogeneous mixing used 200 runs.

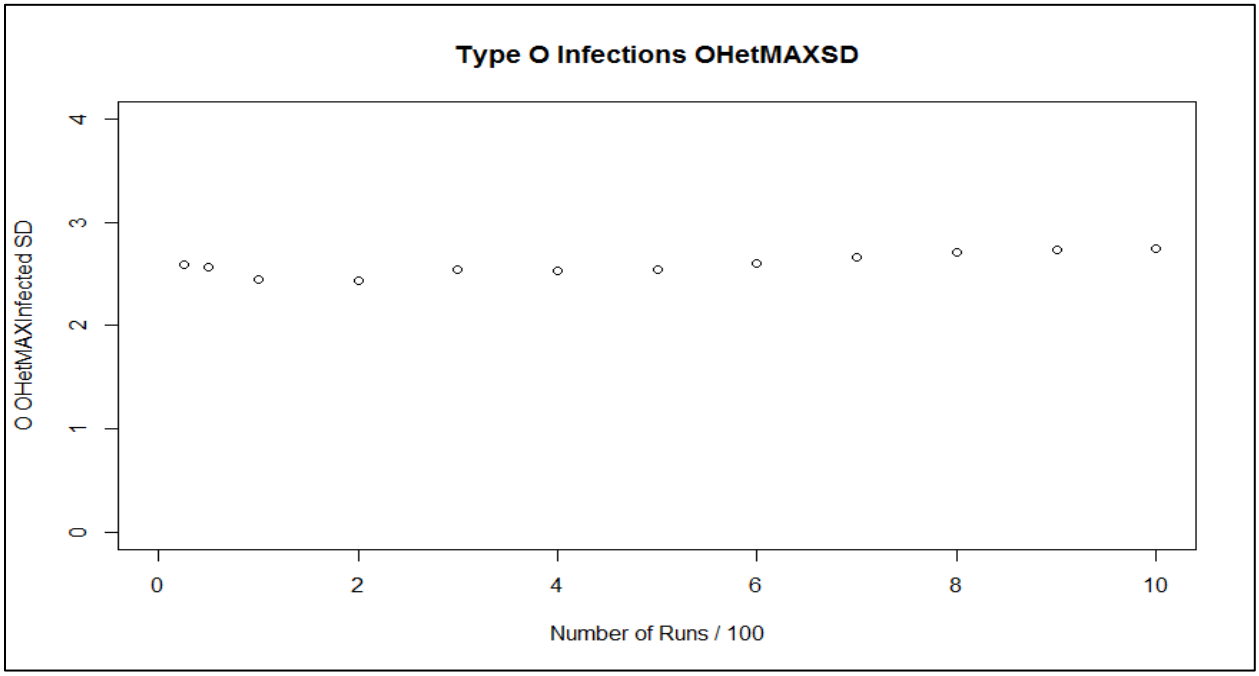

Fig. 6. Heterogeneous Mixing Experiment – standard deviation of the maximum number of herds infected between runs. Looking at this figure, the point at which the standard deviation among maximum number of herds infected

begins to level off starts around 100 runs. For equal comparisons to homogeneous mixing experiments, the number of runs was extended to 200 runs for all future experiments containing heterogeneous mixing.

Cross-Immunity Experiments

Based on our simulations, I was able to conclude that cross-immunity does not prevent FMD infections in the current model. When comparing the percentages of herds that were infected with serotype O and serotype A for each varied cross-immunity experiment, there was little difference in herd infection and immunity among the varied levels of cross-immunity O and cross-immunity A (Fig. 7-9). The different introduction times of serotype A seemed to have no effect on how either a serotype O or a serotype A infection would occur, and the only variable infection observed was when serotype A was introduced at day 494. Another interesting discrepancy in the model to note is that infections of a serotype would only occur once, rather than remain in the herd populations at a low level and have recurring outbreaks. This rise and fall in infections is common for FMD serotypes in Cameroon, but the model did not recreate this phenomenon over the ten-year span (Pomeroy et al. 2015). I believe this discrepancy was caused by the limited number of infections that occurred in the simulations, as there were not enough herds becoming infected to maintain a baseline rate of infection within the population.

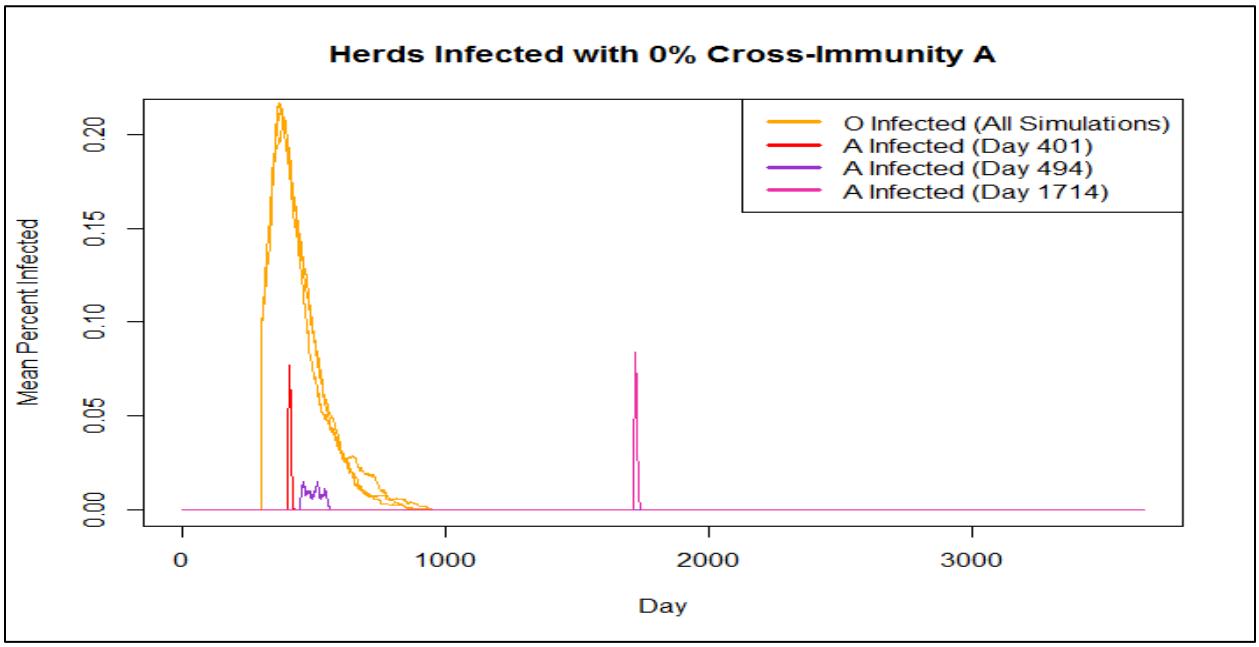

Fig. 7. Mean percent of herds infected when cross-immunity for A was varied at 0%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

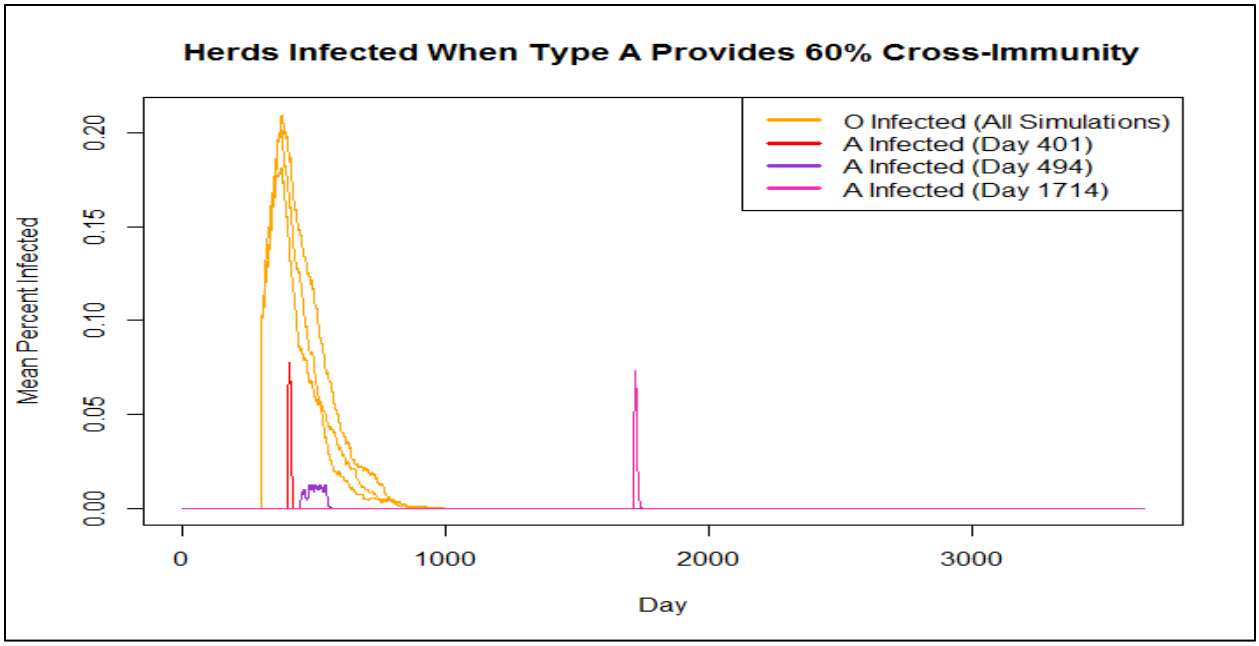

Fig. 8. Mean percent of herds infected when cross-immunity for A was varied at 60%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

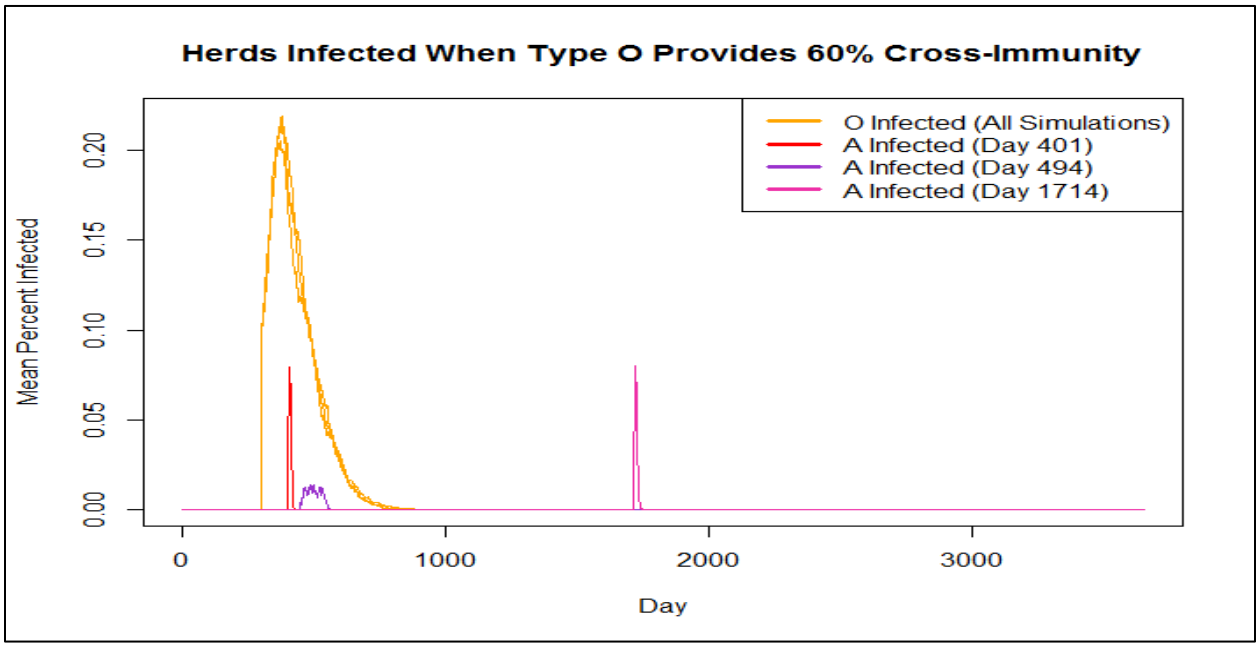

Fig. 9. Mean percent of herds infected when cross-immunity for O was varied at 60%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714

Discussion

Research regarding FMD serotype cross-immunity is sparse, but the consensus in the scientific community appears to be that infections with one serotype do not prevent infection with other serotypes (Jamal and Belsham 2013). The results of our cross-immunity experiments corroborate these

findings, as the level of cross-immunity for serotype O and A had little effect on how outbreaks occurred. This finding would point toward a heavier reliance on vaccination to prevent infections, regardless of the setting and the serotypes that interact within it. However, studies looking into other viral diseases such as measles have found that vaccination may only push back the age at which an individual's immunity wanes, while other studies have found that vaccinating cattle against viruses like peste des petits ruminants could also provide protection against rinderpest due to the interplay of cross-immunity between the viruses (Grenfell and Harwood 1997; Holzer et al. 2016). These viral diseases may not be closely related to the FMD virus, but they show that vaccination has its limits and that even viruses that cause different diseases can have some level of cross-immunity occurring between them.

While conclusions have been drawn from the current simulation runs regarding the lack of effect cross-immunity has on FMD outbreaks, I believe that there are several avenues of this research that should be expanded upon before dismissing the potential effects of cross-immunity altogether. Manipulating model variables like per contact direct infection probabilities, environmental infection probabilities, or herd death and reproduction rates and running experiments with these changed variables could lead to different outcomes regarding cross-immunity. Another important change that could lead to different simulation outcomes would be increasing number of herds used in the model, or changing the model to use individual cattle rather than herds. Shifting from herd to individual level or simply increasing the number of herds may slow simulations considerably due to the large number of cattle in Cameroon, but increasing the number of herds in the model would increase the likelihood of spreading FMD. The increased number of herds would increase the number of contacts susceptible herds would have with infected herds, thereby increasing the probability that susceptible herds would become infected with a serotype while also increasing the number of infections taking place overall. By increasing the number of infections taking place in simulations, multiple outbreaks if different serotypes would be more likely to interact and these increased interactions could possibly yield new results from the model regarding the effect of cross-immunity. Also, to make the model more realistic, the model could be tested against additional disease transmission data from Cameroon and more realistic movement of herds could be simulated. A more realistic model may have added complexity and less applicability to other disease research; however, with these changes and more empirical research regarding cross-immunity conducted, I would hope to yield more concrete conclusions about the FMD cross-immunity at the population level in endemic settings.

Additional Figures

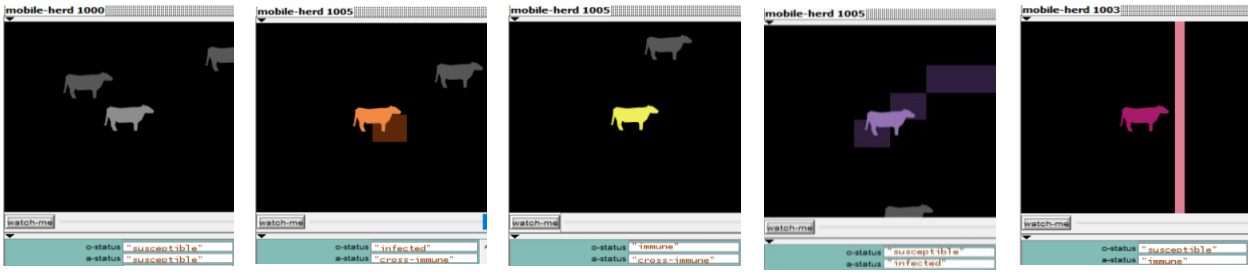

Fig. 10. From left to right: susceptible herd, herd infected with O, herd immune to O, herd infected with serotype A, herd immune to serotype A.

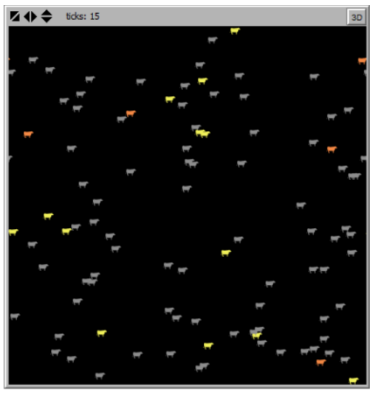

Fig. 11. Snapshot of cattle model as a serotype O infection is taking place.

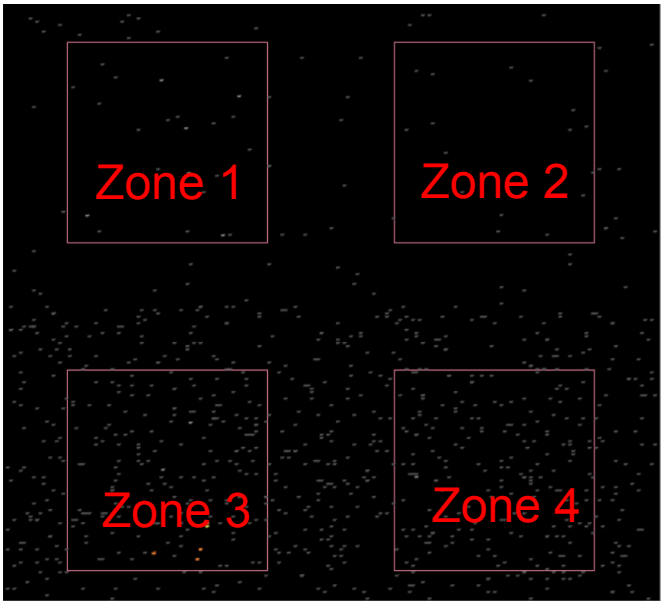

Fig. 12. Snapshot of herd model as a serotype O infection is taking place.

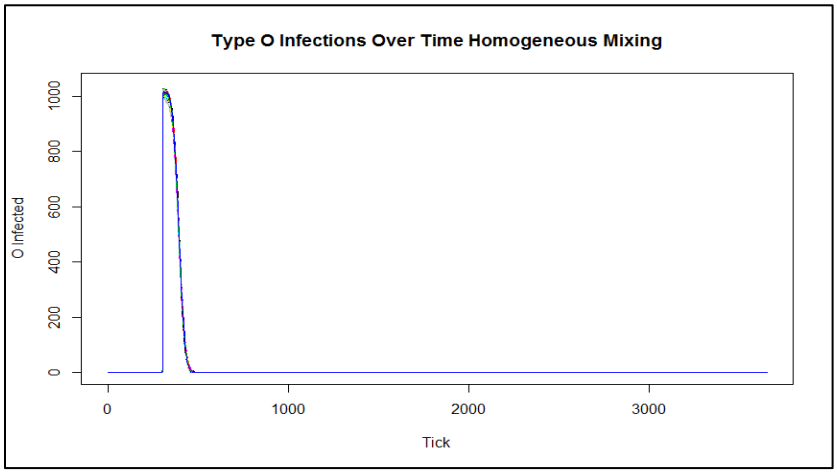

Fig. 13. Homogeneous Mixing Experiment (100 runs) – number of infected herds recorded over time in days

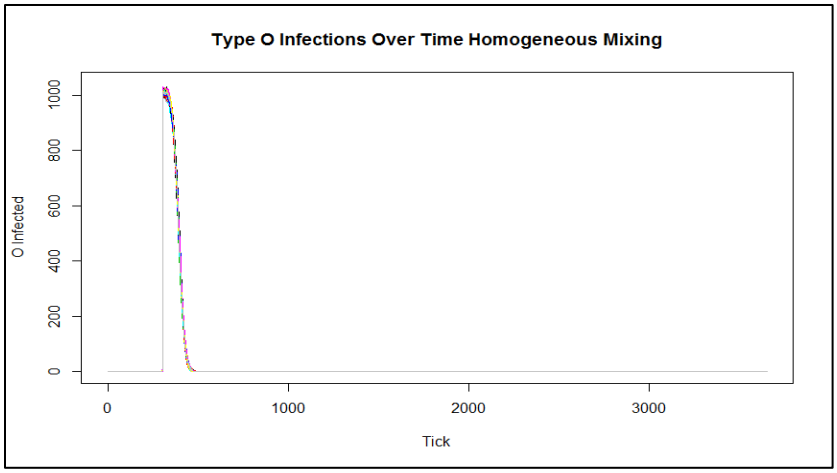

Fig. 14. Homogeneous Mixing Experiment (200 runs) – number of infected herds recorded over time in days

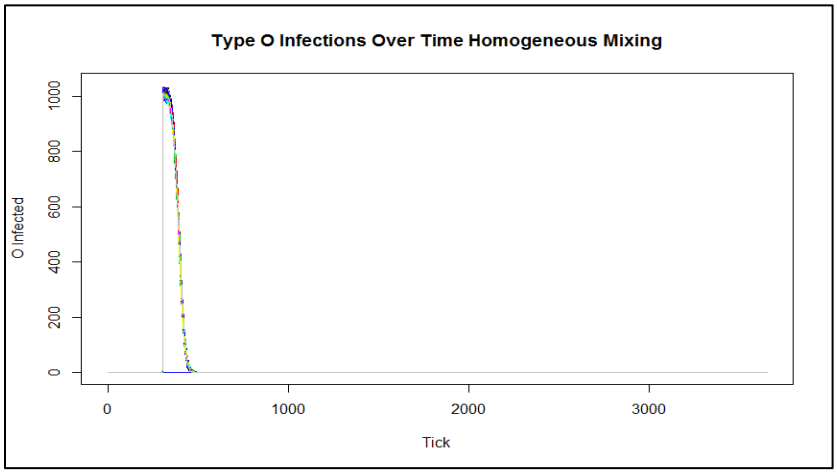

Fig. 15. Homogeneous Mixing Experiment (1000 runs) – number of infected herds recorded over time in days

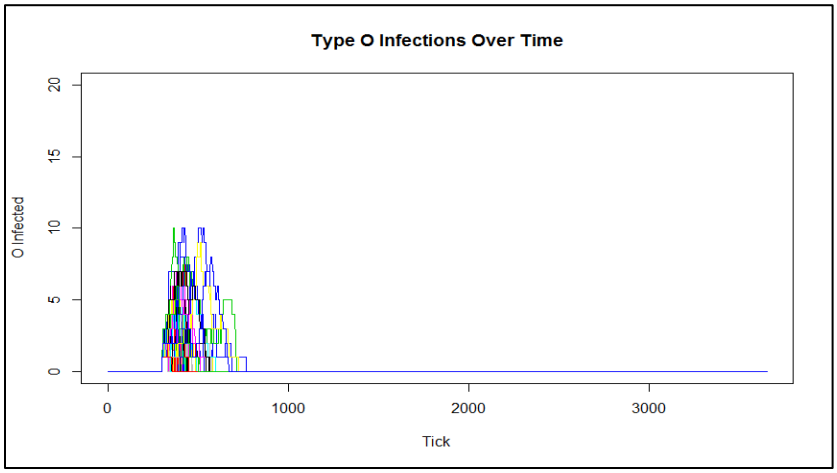

Fig. 16. Heterogeneous Mixing Experiment (100 runs) – number of infected herds recorded over time in days

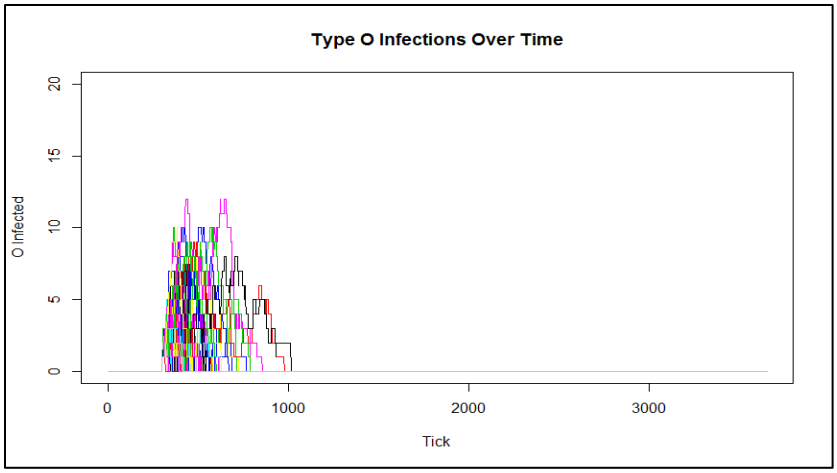

Fig. 17. Heterogeneous Mixing Experiment (200 runs) – number of infected herds recorded over time in days

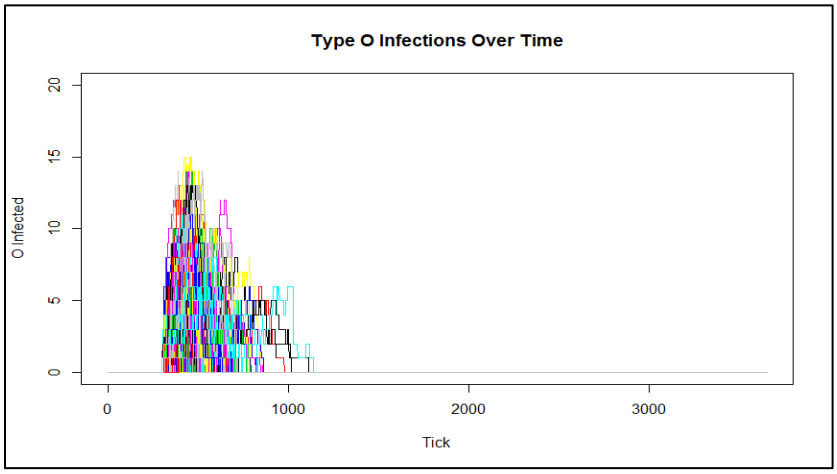

Fig. 18. Heterogeneous Mixing Experiment (1000 runs) – number of infected herds recorded over time in days

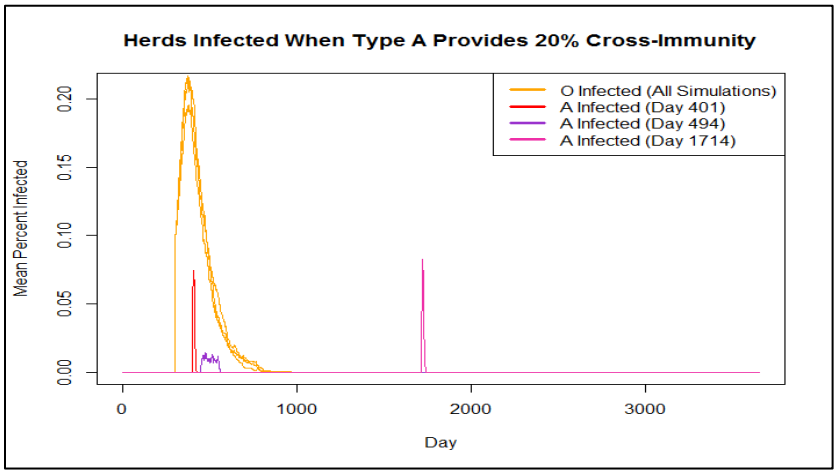

Fig. 19. Mean percent of herds infected when cross-immunity for A was varied at 20%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

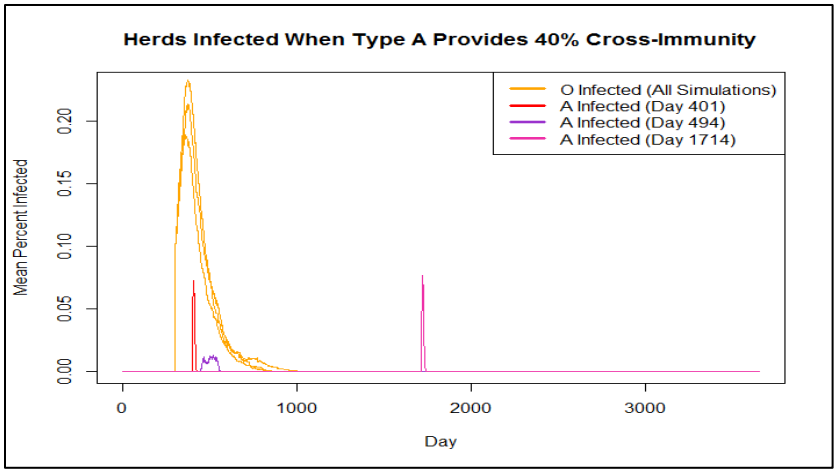

Fig. 20. Mean percent of herds infected when cross-immunity for A was varied at 40%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

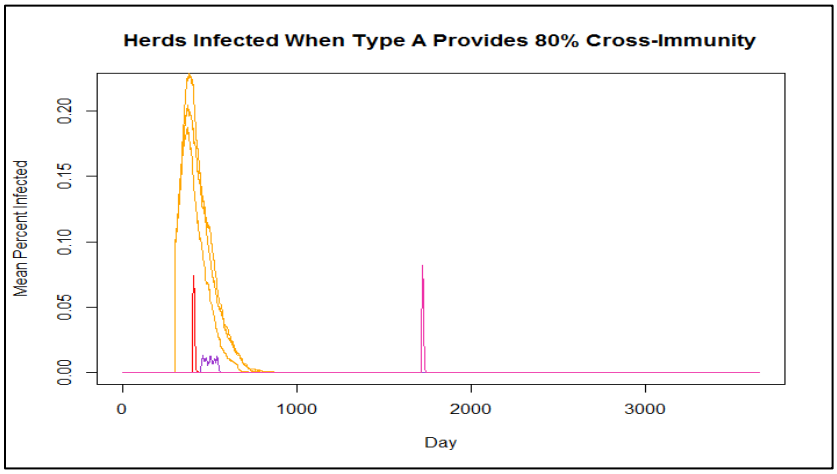

Fig. 21. Mean percent of herds infected when cross-immunity for A was varied at 80%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

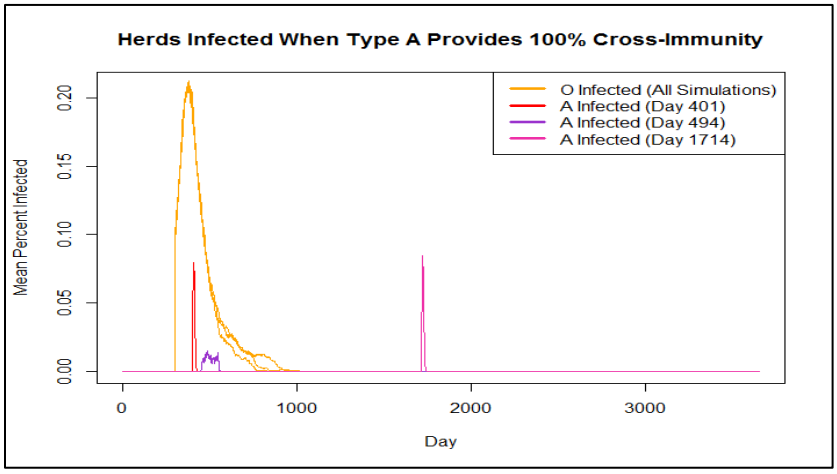

Fig. 22. Mean percent of herds infected when cross-immunity for A was varied at 100%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

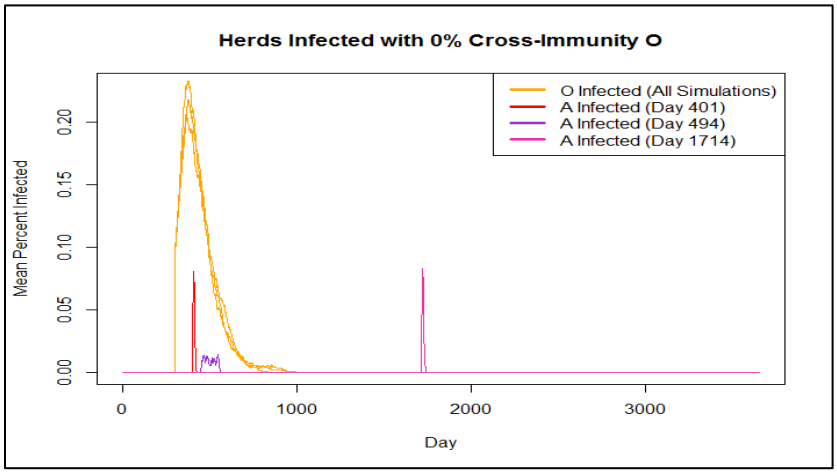

Fig. 23. Mean percent of herds infected when cross-immunity for A was varied at 0%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

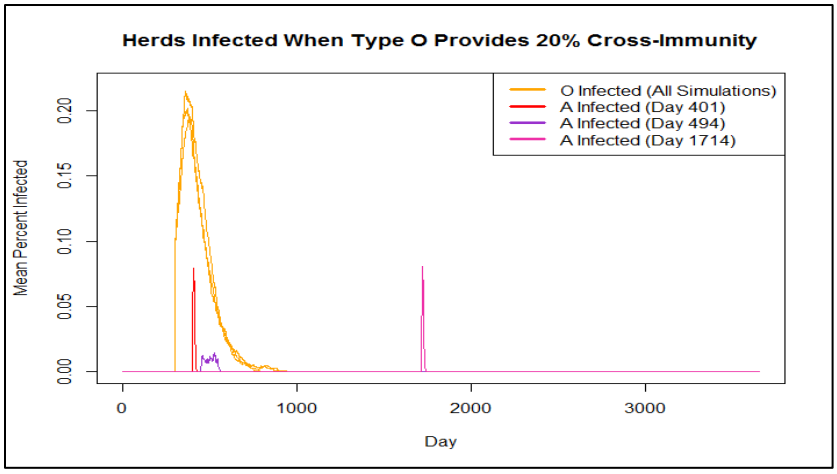

Fig. 24. Mean percent of herds infected when cross-immunity for O was varied at 20%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected

with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

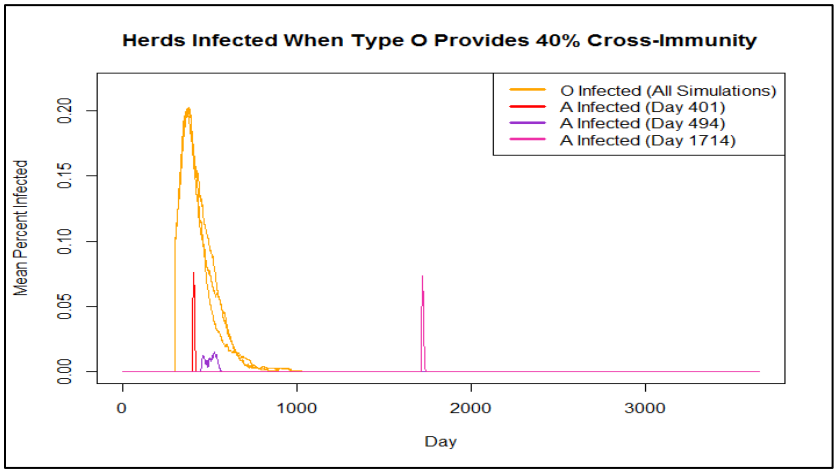

Fig. 25. Mean percent of herds infected when cross-immunity for O was varied at 40%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

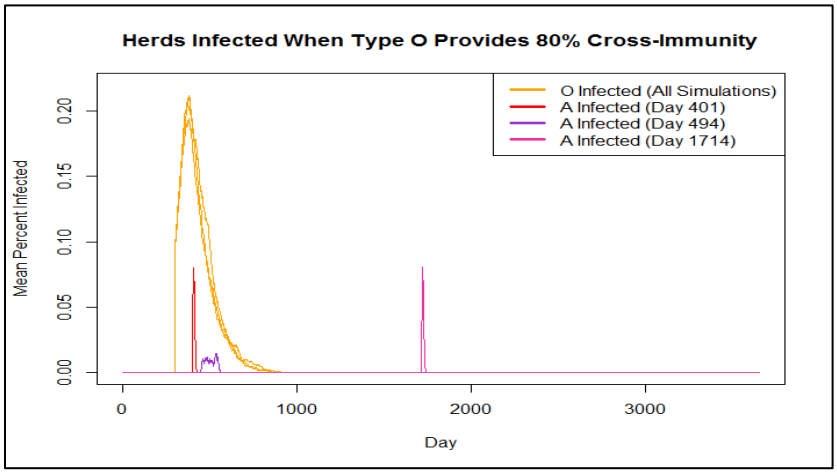

Fig. 26. Mean percent of herds infected when cross-immunity for O was varied at 80%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

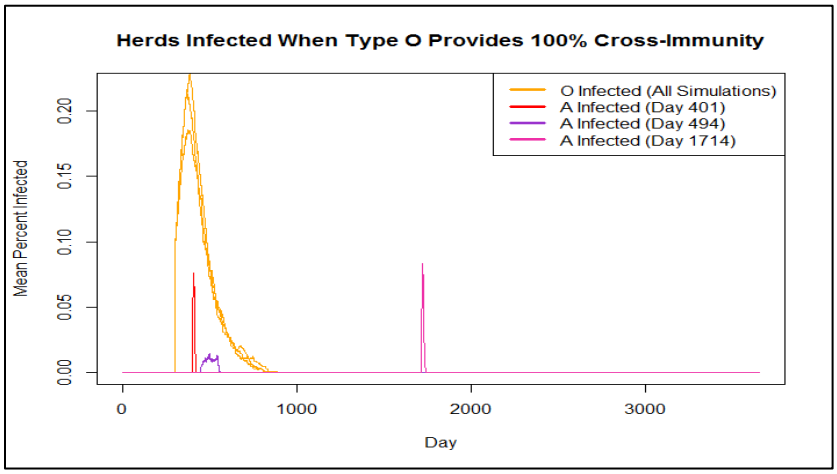

Fig. 2. Mean percent of herds infected when cross-immunity for O was varied at 100%. Mean percent of herds infected with serotype O are depicted in orange for each of the serotype A introductions, while the herds infected with serotype A are depicted in red, purple, or pink for introduction days 401, 494, and 1714.

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